Pistachio Antioxidants Can Decrease Negative Effects of Free Radicals on Male Reproductive System: An Assessment and Review

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Abstract

Oxidative stress (OS) has been identified to be an important cause of sperm dysfunctions. Abnormal sperm morphology, chromatin integrity and DNA may have adverse effects on the implantation and early embryo development. Antioxidants are capable of scavenging or neutralizing reactive oxygen species (ROS) and then alleviating OS. Spermatozoa are particularly susceptible to ROS, because of the loss of a large amount of their cytoplasm along with its antioxidant content during the process of spermiogenesis. Normally, the level of seminal ROS is restricted by seminal antioxidants, but enhanced pathological ROS generation leads to OS and then sperm abnormality. Some nutrients including nuts, fruits are antioxidant rich. Pistachio is one of main antioxidants source. Pistachios contain high levels of antioxidants and studies showed pistachio have positive and protective effects on male reproductive system. In this review we will discuss the influence of ROS on sperm DNA damage and protective role of pistachio antioxidants

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1. Introduction

Sperm DNA contains half of the genetic material that is effective in reproduction, and any abnormality in sperm genome can lead to the reproductive process failure (1). Although sperm DNA damage in infertile men has been identified, it has been reported in relation with the spermatogenesis phase, but sperm DNA damage in low grade has also been reported in fertile men (2). The causes of injury to sperm DNA were different and intra-and extra-testis factors can be effective on sperm DNA damage (3).

Intra-testis factors include age, congenital anomalies such as cryptorchidism, genetic disorders, and idiopathic abnormalities (4). The studies were showed increases in age were in relation of decrease in sperm parameters (5, 6). Extra testicular factors include smoking, alcohol consumption and drug abuse by production of Reactive Oxygen Species (ROS) can reduce the quality of semen and reducing the sperm concentration, motility and morphology and increase in Sperm DNA damage (7).

Cancer in men (Hodgkin's lymphoma and testicular tumors) showed reduced levels of semen quality and increased level in sperm DNA damage before treatment (8). Inflammation and infection of the reproductive organs, such as prostatitis and epididymitis, can increase the leukocytes in the semen (leukocytospermia) and, consequently, increase the level of reactive oxygen species (ROS), which can leads to damage to the DNA (9). Fever with increased testicular temperature (hyperthermia) causes damage to sperm DNA and increases the histone to protamine ratio in sperm chromatin(10). Some lifestyles condition and behaviors, such as the use of saunas and hot baths, the use of laptops, as well as some jobs, such as welding, bakeries, prolonged driving, are accompanied by increased scrotal temperature, which can credited sperm DNA damage (11, 12)

Studies have shown that people who are exposed to pesticides, phthalates, and metals such as cadmium, lead, and infection had an increased level of oxidative stress and sperm DNA damage (13-15). Also, studies have been reported the relationship between varicocele and high level of oxidative stress and sperm DNA damage in semen (16, 17).

Antioxidants, are capable of scavenging or neutralizing reactive oxygen species (ROS) and then alleviating Oxidative stress (OS). Some nutrients including nuts, fruits are antioxidant rich. Pistachio is one of main antioxidants source and have positive effects on reproductive system. In this review we will discuss the influence of ROS on sperm DNA damage and protective role of pistachio antioxidants.

2. Materials and Methods

We reviewed the clinical trials related to the effects free radicals on the sperm DNA damage and all studies related to pistachio and male reproductive system, sperm parameters, hormonal profile and DNA damages. Studies searched in PubMed with the key words antioxidant, sperm parameters, sperm DNA damage, pistachio. Then related studies to the aim of this paper included and the results assessed and discussed.

3. Discussion

ROS includes all reactive molecules that contain oxygen, including free radicals. There was several types of ROS include hydroxyl radical, anion superoxide radical, hydrogen peroxide, oxygen radical, nitric oxide (NO), hypochlorite and various lipid peroxides. These factors can create cellular damage by react with cell membrane lipids, nucleic acids, proteins, enzymes, and small molecules (16, 18). On the other side ROS has positive effects in biological activities. One of the biological roles can be its role as the intracellular messenger and the regulation of gene expression, especially the gene related to antioxidant proteins. Therefore, the presence of ROS is necessary for normal cell function, and any change in the physiological level causes oxidative stress and unsafe for cell survival (19).

Oxidative stress and sperm

Oxidative stress occurs when ROS level is higher than antioxidant level. In pathologic conditions in the male reproductive system, oxidative stress significantly defect spermatogenesis process and sperm function, which may lead to male infertility. ROS can induction the lipid peroxidation in the plasma membrane of the sperm that effect on the flexibility of the membrane and its movement. In addition, ROS may affect sperm axoneme and impaired mitochondrial function and also can effect on the DNA, RNA, and proteins synthesis (14, 20)

Approximately 40% to 80% of infertile patients have high levels of ROS in their semen (21). The high levels of ROS production in seaman attribute to semen leukocytes and abnormal sperm in semen (16). The production of ROS in spermatozoa may be due to the Nicotinamide adenine dinucleotide phosphate (NADPH) on the surface of the plasma membrane of sperm or Nicotinamide adenine dinucleotide (NADH) on oxidative reductase in the mitochondrial surface (22). Oxidative stress can create abnormal DNA denaturation, and fracture inn single-stranded or double-stranded DNA, chromatin cross-linking and small chromosomal deletions (15).

Sperm motility is essential for nature sperm function, to pass female reproductive tracts, penetrate to the oocyte and fertilization. Several studies have been shown negative correlations between high levels of ROS and reduced sperm motility, morphology and sperm function (23, 24). The effects of ROS are dependent on nature, quantity, time of action and duration of exposure to ROS (25). Sperm with residual cytoplasm has high cellular content with a variety of cytoplasmic enzymes, including lactic dehydrogenase (G-6-PDH). All of this enzymes are associated with sperm function defects. Dissimilar other cells, spermatozoa has a unique and highly sensitive structure to ROS. Fatty acids in the sperm plasma membrane provides fluid for the normal sperm activity (26).

The peroxidation of sperm unsaturated fatty acids leads to the formation of endogenous toxic products such as 4-hydroxy-2-nonenal (4-HNE) and malondialdehyde (MDA), which accumulation has a negative effect on the results of the hamster zona-free ovum test (HZFO test) (27, 28). The attack of radicals on sperm unsaturated fatty acids can disrupts sperm membrane structure, fluidity and its functional quality, which can effect on the ability of spermatozoa at the penetration step, such as acrosome reaction and oocyte penetration (20, 29).

Antioxidants

Wherever there were free radicals, antioxidants are the main way to ell defect and repairing damaged cells. Because antioxidants are responsible for eliminating free radicals and increasing the body immune system against a variety of diseases (30).

Antioxidant is a molecule can inhibit or slow down the process of oxidation in other molecules. Oxidation is a chemical process that transports the electron from a substantial to an oxidizing agent. Free radical oxidation can start a chain reactions that cause damage to cells. Antioxidants, by removing intermediate free radicals, terminate these chain reactions and, by oxidizing themselves, prevent oxidation of other molecules (31). Although the oxidation is necessary for life, these reactions can be harmful, however, plants and animals have multiple and complex systems of antioxidants such as glutathione, vitamin C and E, as well as enzymes such as catalase, superoxide dismutase, and several types of peroxidase (32).

Antioxidants are widely used in food supplements for the health and prevention of cancer and coronary artery disease (33). Several studies found that antioxidants are beneficial for health (34, 35). In addition to medical usages, antioxidants are also used in the industry including food preservatives and cosmetics and Anti-corrosion (for metals) (36). Early studies focused on the role of antioxidants in biology and the prevention of oxidation of unsaturated fatty acids. By identifying vitamins E, C, A, as antioxidants, a great alteration was created in the function and role of antioxidants in the biochemical of living organs (37, 38).

Pistachio is one of main antioxidants source

Compared to other nuts, pistachios contain high levels of antioxidants, including lutein, β-carotene, γ-tocopherol, chlorophylls, isoflavones, proanthocyanidins, anacardic acids, cardanols and also vitamin C and selenium (39, 40). They have a relatively high in vitro antioxidant capacity (41). These antioxidants can play an important role in the biological antioxidant network and with their synergistic effects can protect the cells against oxidative damage. Kocyigit A et al., Found beneficial effects on serum antioxidant levels in men and women who received 20% of their energy from pistachios for three weeks (42).

Another study found that a heart-healthy diet including pistachios reduced the serum oxidized-LDL concentration and significantly increased the serum concentrations of γ-tocopherol, lutein, and β-carotene and the researchers concluded that pistachio can have a beneficial effect on serum antioxidants (39).

The role of pistachio on testis tissue

Pistachio can affect testicular tissue with the vitamins that it contains. Administration of 10 mg/kg of bene powder (a species of pistachio) to Busulfan- induced infertile mice for 35 days resulted in reduction of oxidative stress and improvement of testicular histopathology (43). In a study, experimental groups received 1, 2 and 4 mg/kg pistachio respectively for 28 days orally. After this period mean number of Sertoli cells, Leydig cells, spermatogonia, spermatocytes and spermatids in different experimental groups did not show any significant difference but sperm density in the seminiferous tubules showed an increasing trend in the experimental groups (44). In another study by Yang et al., They found that vitamins B, C, E were helpful in reducing the toxic effects on testicular tissue (45).

The role of pistachio on seminal fluid

Seminal fluid is one of the antioxidant sources, and a main protective system against oxidation damage. Antioxidants in the semen are include vitamins E and C, superoxide dismutase, glutathione, lycopene and thioredoxin (46). Several studies have examined the relationship between antioxidants and the DNA damage and have shown that reducing the antioxidants of the seminal fluid is associated with DNA defects and damage (47, 48), but others have not found any relationship (49, 50).

Several review studies have shown that a healthy diet rich in ω-3 antioxidants (e.g., vitamins C and E, selenium, and zinc), carnitines, and folate may improve semen quality and male fertility (51, 52). Pistachio is a nutrient- dense food rich in some of the above mentioned nutrients. So it is possible that it may improve semen quality and sperm parameters by elevating these substances in semen.

The role of pistachio on male hormone profile

Zn is a vital nutrient for pistachios and it is an essential element involved in male reproduction. In a study that conducted by Shariati et al. revealed that edible pistachio oil increases the level of testosterone (44). In a study, the relationship between serum levels of testosterone, selenium, and zinc was evaluated in two groups of infertile and fertile men. The results showed a significant difference in the mean serum Zn, Se and testosterone in comparison between the two groups (53).

The zinc transporter (ZnT) family is involved in the maintenance of Zn homeostasis. Zhao et al. revealed that ZnT7 may possibly play an important role in regulating testosterone synthesis through the steroidogenic enzymes and severe zinc deficiency may cause zinc depletion in the semen fluid, which results in decreased the level of testosterone and inhibits spermatogenesis (54).

Pistachios contains high amounts of oleic and linoleic acids. These enzymes are able to inhibit the 5 alpha reductase enzyme (55). 5 alpha reductase is important for converting testosterone to dihydrotestosterone (56). Thus, by inhibiting this enzyme, the conversion of testosterone to dehydrotestosterone decreases and as a result the level of testosterone in the blood can be reduced.

The role of pistachio on sperm parameters

Antioxidants such as vitamins E, C, glutathione, catalase, albumin and Superoxide dismutase (SOD) prevent decrease in sperm motility (29), and antioxidants such as cysteine and Q-10 coenzyme increase motility of sperms (57). In asthenospermia patients, incubation of sperm sample for 24 hours in Hams F-10 medium plus 50 micromoles of Q-10 coenzyme can improves sperm motility. Oral use of carnitine at 2-3 grams daily, more than two months, can increase the sperm count and mobility (1, 58).

Albert Salas-Huetos et al. evaluated the effect of chronic consumption of nuts on sperm parameters. They found the improvement in total sperm count, motility, vitality, progressive motility and morphology in experimental group compared to control group. The nut group showed a significant reduction in sperm DNA fragmentation but they did not found significant changes in ROS and sperm chromosome anomalies between groups (59).

Few studies have been conducted on the effect of pistachios on sperm parameters. In a study, the researchers investigated the effect of pistachio by - products (PBP)on sperm quality parameters and fatty acid composition in Farahani rams. They confirmed that adding 12.5% PBP to the diet has no detrimental effects on sperm parameters (60). Another study indicated a significant increase in sperm motility, normal morphology and viability rate in infertile mice model by administration of 10 mg/kg of bene (pistacia atlantica) powder for 35 days (43).

Pistachio role on sperm membrane lipid peroxidation

In 1989, Aitken reported a decrease in sperm motility by increasing in membrane lipid peroxidation (61). Again, in another study reported that seminal fluid antioxidants can prevented the peroxidation of sperm membrane lipid (62). Kobayashi reported in 1991 the addition of antioxidants such as 400 IU/ m Superoxide dismutase (SOD) was effective to prevent of sperm lipid peroxidation (63). Rolf and his colleagues found that 10 and 800 µmol / L of vitamin E were effective in protecting sperm lipid peroxidation (64).

Pistachios are an excellent source of antioxidants, including lutein, beta-carotene, and gamma-tocopherol (Penn State News, 2010). gamma-tocopherol is used as a precursor to vitamin E. Oral administration of vitamin E leads to significantly decrease in the malondialdehyde (MDA) concentration in spermatozoa (65). Administration of vitamin E as an antioxidant to protect against Reactive Oxygen Specious (ROS) decreases the lipid peroxidation (LPO) and leads to positive effects on sperm parameters such as sperm motility and concentration (66).

Sperm is highly sensitive to oxidative stress due to the abundance of unsaturated fatty acids in the membrane which leads to oxidative damage and it effect on sperm motility, fluidity of the membrane and fertilization ability. In a study was examined the protective effects of bene extracts (pistacia atlantica) on hepatotoxity in rats. They found a decrease in the amount of ROS and prevent liver damage as an antioxidant by decreasing MDA and increasing the antioxidant level of superoxide dismutase and catalase enzymes (67). Hojat Norasteh et al. found in their study that bene administration decreased the level of malondialdehyde and increased the level of superoxide dismutase and catalase enzymes in infertile mice model. Also Reduction of malondialdehyde can prevent the lipid peroxidation of sperm membranes (43).

The role of pistachio in preventing DNA damage

Many studies have shown that antioxidants can reduce DNA fragmentation due to oxidative stress (68, 69). Daily intake of vitamins E and C for two months reduces the count of positive TUNEL sperms from 22.1% to 9.1%. However, in the control group, the TUNEL positive sperm was 22.4%. Progresses with this form of treatment have had a significant effect on the success pregnancy rate from 6.9% to 48.2% and implantation rate from 2.2% to 6.9% (70).

Adding vitamin C or E to a sperm media also preserves its DNA from damage caused by multiple centrifuges (71). Albumin also protects the lipid peroxidation from defects to the sperm plasma membrane and DNA (72). Abad and colleagues conducted a study on 20 infertile patients with terato-asthenozoospermia. They either takes to patients orally prescribe pills containing a combination of creatinine, vitamin E, C, B9, B12, quinidine Q10 and selenium anti-oxidants for three months daily. The results of their study showed that not only the sperm parameters were improved, but also sperm DNA integrity increased and DNA fragmentation were decreased in study group. They discussed that in men oral administration of antioxidants for 3 mounts could improve assisted reproductive techniques (ART) outcome (73).

In another study, 38 infertile men with high level of fragmented DNA (15%≤) received vitamin E and C for 2 months daily and results showed reduction of DNA fragmentation in 76% of patients. It also indicated that this treatment improves the intra-cytoplasmic sperm injection (ICSI) outcome in patients with high sperm DNA fragmentation (74).

Raigani et al. showed oral administration of zinc sulfate to infertile patients, significantly improved the DNA integrity (75). In a study, infertile patients with high level of oxidative stress, ROS, and Sperm DNA fragmentation treated with capsules containing a combination of vitamin E, C, zinc, selenium and folate for 3 months. After this time, the DNA fragmentation was evaluated by TUNEL, apoptosis assessed by Annexin V, protamination with CMA3 and ROS production with Nitro blue tetrazolium. The results showed a significant improvement in DNA fragmentation and protamine deficiency. They also reported a decrease in the production of ROS and apoptosis, but did not see any significant changes in the improvement of sperm parameters (76).

Patients with varicocele are most commonly with high level of DNA fragmentation. A study was done on 20 infertile patients with grade 1 varicocele. In this study, patients were taken a combination of several supplements including L-carnitine, vitamins C, E, B9, Zinc B12, selenium, and coenzyme Q10 for 3 months orally. After treatment, patients showed a 22.1% reduction in DNA fragmentation (77).

Zini and colleagues planed an in vitro study. In their study, after semen samples from 12 infertile patients were placed under oxidative stress by H2O2. In case group, samples incubated with lycopene (5 µmol) for 2 hours before induction of oxidative stress. Comparison between case and control group showed that lycopene can protect the sperm from degradation of DNA, but cannot improve its slow motility (78).

Several studies have shown that antioxidants are able to protect the sperm DNA from endogenous free radicals (79- 81) and exogenous free radicals (82, 83). In ART andrology lab, the semen sample should first be washed. This process raises free radicals and destroys DNA. Studies have been planned to reduce these negative effects. However, the protective effect of antioxidants on sperm DNA is limited (84), and in a study showed antioxidants intake (such as a combination of vitamins C, E) were the cause of DNA fragmentation (85).

In ART, it is sometimes necessary that the sperm should be frozen and thaws at the right time, but this process has a negative effect on sperm DNA. Studies have been conducted to reduce this degradation. Several studies have shown a positive protective effect of antioxidants against oxidative damage on sperm DNA during freezing and thaw (86, 87). In contrast, Tylor et al. showed a negative effect of vitamin E on the excretion of sperm DNA in the process of freezing and thaw in their study (88). In general, documents indicates that antioxidants are effective in the protection of the sperm in the process of freezing and thaw, but the freezing method and the type of cry protectant used in this procedure are important (89).

There are many new antioxidants that can reduce the level of oxidative stress, and improve the quality of sperm, but lack of scientific evidence of their effectiveness and FDA approval are main cause of limitation to use. However, oxidative stress is only one of the causes of male fertility disorders and it is suggested that anti-oxidant therapy should only be used if oxidative stress causes DNA damage (90- 92).

There are studies that have shown that pistachio can increase the activity of endogenous antioxidant enzymes (93). Chronic consumption of pistachios reduces DNA damage and enhances the gene expression of some genes associated with telomeres, which can promote human health (94). Telomeres are highly sensitive to oxidative stress due to their abundant guanine (95). Nuts are rich in a variety of vitamins, polyphenols and phytosterols with antioxidant and anti-inflammatory properties and have a positive effect on telomeric chromosomes (96). Gama tocopherol is a predominant type of vitamin E, which is abundantly found in pistachios and has anti-inflammatory and antioxidant properties (97). Vitamin E was able to neutralize free radicals and protect sperm against them, thereby reducing DNA damage (31). In a study on pistachios, Glei and colleagues found that pistachio FS (Fermentation supernatants) can significantly reduce levels of H_2O_2-induced DNA damage (98). This decrease can be due to the compounds present in pistachio including bioactive phytochemicals (e.g., phenolic acid, proanthocyanidins, flavonoids and γ-tocopherol) (99). In another study indicated that pistachios have chemopreventive properties by inhibiting growth of adenoma cells and reduces the levels of DNA damage (100).

4. Conclusion

According to studies that have been published, antioxidants can reduce the sperm DNA fragmentation, especially in people who have high-level of DNA damage. Since the causes of infertility are various, the lack of antioxidants action in reducing the sperm DNA damage, the level of antioxidant activity depends on the type, dose and duration of intake. Pistachios contain high levels of antioxidants and studies showed pistachio have positive and protective effects on male reproductive system. Although more studies are needed to determine the appropriate pistachio dose of administration on all parts of male reproductive system.

Conflicts of Interest

There are no conflicts of interest.

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Table 1: Summary of studies about pistachio and sperm cell

	Reference	Conclusion
Pistachio is one of main antioxidants source	kay (201o) (39) preedy (2011) (40)	Pistachios contain high levels of antioxidants, including lutein, β-carotene, γ-tocopherol, chlorophylls, isoflavones, proanthocyanidins, anacardic acids, cardanols and also vitamin C and selenium.
The role of pistachio on testis tissue	Norasteh (2019) (43)	10 mg/kg of bene powder (a species of pistachio) for 35 days in mice can reduced oxidative stress and improvement of testicular histopathology.
	Shariati (2013) (44)	1, 2 and 4 mg/kg pistachio respectively for 28 days orally have positive effects on sperm density in the seminiferous tubules
The role of pistachio on seminal fluid	Salas- huetos (2017) (51)	Diet rich in ω-3 antioxidants can improve semen quality and sperm parameters by elevating these substances in semen.
	Giahi (2016) (52)	Diet rich in ω-3 antioxidants (e.g., vitamins C and E, selenium, and zinc), carnitines, and folate may improve semen quality.
The role of pistachio on male hormone profile	Shariati (2013) (44)	Edible pistachio oil increases the level of testosterone.
	Abe (2009) (55)	Pistachios contains high amounts of oleic and linoleic acids. These enzymes are able to inhibit the 5 alpha reductase enzyme and promote hormone syntheses.
	Avendano (2018) (56)	5 alpha reductase is important for converting testosterone to dihydrotestosterone.
The role of pistachio on sperm parameters	Salas- huetos (2018) (59)	Nuts can improve total sperm count, motility, vitality, progressive motility and morphology.
	Khodaei-Motlagh (2019) (60)	Adding 12.5% pistachio by- products to the diet has no detrimental effects on sperm parameters.
	Norasteh (2019) (43)	Significant increase in sperm motility, normal morphology and viability rate ocured in infertile mice model by administration of 10 mg/kg of bene (pistacia atlantica) powder for 35 days
Pistachio role on sperm membrane lipid peroxidation	Tolooei (2015) (67)	Bene extracts (pistacia atlantica) on hepatotoxity in rats can decrease in the amount of ROS and prevent liver damage as an antioxidant by decreasing MDA and increasing the antioxidant level of superoxide dismutase and catalase enzymes.
	Norasteh (2019) (43)	Bene administration decreased the level of malondialdehyde and increased the level of superoxide dismutase and catalase enzymes in infertile mice model
	Canudas (2019) (94)	Chronic consumption of pistachios reduces DNA damage and enhances the gene expression of some genes associated with telomeres, which can promote human health.
	Glei (2016) (98)	Pistachio FS (Fermentation supernatants) can significantly reduce levels of H_2O_2-induced DNA damage.
	Glei (2017) (100)	Pistachios have chemopreventive properties by inhibiting growth of adenoma cells and reduces the levels of DNA damage.
The role of pistachio in preventing DNA damage	Boating (2016) (93)	Psistachio can increase the activity of endogenous antioxidant enzymes